Potent Dual Plasmepsin IX/X Inhibitors towards the Treatment of Malaria

Malaria is a devastating disease affecting ~240 million people annually around the globe resulting in >600,000 malaria-related deaths. Drug resistance to first-line antimalarials, including artemisinin, is increasing resulting in a critical need for the discovery of new agents with novel mechanisms of action. In collaboration with the Walter and Eliza Hall Institute and with funding from the Welcome Trust a phenotypic screen of Merck's aspartyl protease inhibitor identified a series of plasmepsin X (PMX) hits that were more potent than chloroquine. Inspired by a PMX homology model, efforts to optimize potency resulted in the discovery of leads that in addition to potently inhibiting PMX, also inhibit another essential aspartic protease, plasmepsin IX (PMIX). Further potency and PK profile optimization efforts culminated in the discovery of advanced leads with potent dual PMIX/X inhibitory activity and excellent rodent pharmacokinetics. These leads have demonstrated robust proof of biology in *in vivo P. berghei* and *P. falciparum* mouse blood stage models of malaria. In addition, they block the liver and mosquito stages of the *Plasmodium* lifecycle and displays an excellent resistance profile.